

# HBeAg-Negative Chronic Hepatitis B: Cost-Effectiveness of Peginterferon Alfa-2a Compared to Lamivudine in Taiwan

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## ABSTRACT

**Objective:** In Taiwan, the carrier rate of hepatitis B surface antigen is 15% to 20%, one of the highest in the world. Among chronic hepatitis B (CHB) patients, hepatitis B e antigen (HBeAg)-negative accounts for approximately 40% to 50% of these patients. A recent study found that peginterferon alfa-2a (40 KD) is more effective than lamivudine in treating HBeAg-negative CHB, but its cost-effectiveness has not been evaluated. Our objective is to evaluate the incremental cost-effectiveness of 48 weeks of peginterferon alfa-2a compared to 48 weeks of lamivudine, from the perspective of the Taiwan Bureau of National Health Insurance. **Methods:** A Markov model was used to simulate the natural history of HBeAg-negative CHB in a cohort of 40-year-old patients. Efficacy, disease progression, economic, and quality-of-life data were derived from published literature and a survey of clinical experts in Taiwan. Life expectancy, quality-

adjusted life expectancy, lifetime costs in New Taiwan Dollars (NTD) (1 USD = 31.96 NTD), and incremental cost-effectiveness ratios (ICERs) were calculated.

**Results:** The gain in quality-adjusted life-years (QALYs) for 48 weeks of peginterferon alfa-2a compared to 48 weeks of lamivudine was 0.45 at an additional cost of 157,000 NTD (4900 USD), resulting in an ICER of 347,000 NTD (10,900 USD) per QALY gained. The 95% central range for the ICER from a probabilistic sensitivity analysis was 228,000–566,000 NTD (7100–17,700 USD).

**Conclusions:** In HBeAg-negative CHB, 48 weeks of treatment with peginterferon alfa-2a compared to 48 weeks of lamivudine appears to offer life expectancy and quality-of-life improvements at an acceptable cost-effectiveness ratio.

**Keywords:** cost-effectiveness, hepatitis B, lamivudine, peginterferon, Taiwan.

## Background

Chronic hepatitis B (CHB) infection is an important public health problem worldwide, with about two billion people having experienced acute infection, of which 350 million have developed chronic hepatitis B virus (HBV) infection. Approximately 75% of the infected persons are in Asia. In Taiwan, the carrier rate of hepatitis B surface antigen (HBsAg) is as high as 15% to 20%, one of the highest in the world [1]. HBV infection is usually acquired from perinatal transmission [2]. In Taiwan, heterosexual contact is also considered an important cause of hepatitis B transmission for susceptible adults [1].

Chronic HBV infection is characterized by the persistence of HBsAg and serum HBV-DNA levels detectable for more than 6 months. Among patients with active viral replication, cirrhosis will develop in 15% to 20% of patients within 5 years [3]. For patients with cirrhosis, the disease may progress, and the incidence of

hepatocellular carcinoma (HCC) is greatly increased (70–90% of HCC patients have cirrhosis) [3]. In a Taiwanese case-control study, the relative risk of developing HCC, compared to non-carriers, was 64.7 for carriers of HBsAg and hepatitis B e antigen (HBeAg) and 17.9 for carriers of HBsAg only [4].

According to the top 10 causes of death published by the Taiwanese Department of Health, chronic hepatitis disease as well as liver cirrhosis caused 5185 deaths (mortality rate: 22.98 per 100,000 population) in 2003, and ranked in the sixth position of the top 10 causes of death [5]. Liver cancer led to 7010 deaths (mortality rate: 31.07 per 100,000 population) in 2003 and was the leading cause of cancer deaths in Taiwan [5]. The economic burden of HBV infection is also substantial because of the high morbidity associated with decompensated cirrhosis and HCC. According to the Bureau of National Health Insurance (BNHI), approximately 5.57 billion New Taiwan Dollars (NTD) (i.e., 173.3 million USD) was spent on the medical care of patients with chronic hepatitis, cirrhosis, and HCC in 2002 [6].

In some patients, HBeAg seroconversion is accompanied by the selection of HBV variants that are

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unable to produce HBeAg. A proportion of these HBeAg-negative (mutant type CHB) patients may later develop higher levels of HBV replication and progress to HBeAg-negative chronic hepatitis. Among CHB patients, HBeAg-negative accounts for approximately 40% to 50% of these patients [1,7,8].

The treatments currently approved and reimbursed by the Taiwan BNHI for patients with HBeAg-negative CHB are interferon alfa and lamivudine. Nevertheless, the majority of the patients treated in Taiwan are treated with lamivudine, making lamivudine the standard of care in Taiwan. Recently, peginterferon alfa-2a (40 KD) also was approved in Taiwan based on a phase III randomized controlled international clinical trial published by Marcellin et al. evaluating the efficacy and safety of peginterferon alfa-2a (40 KD) combined with placebo or lamivudine versus lamivudine alone in HBeAg-negative patients with CHB [9]. A total of 552 patients were enrolled in the study, 61.8% of whom were Asian. Patients were treated for 48 weeks with a 24-week treatment-free follow-up period. Significantly more patients treated with peginterferon alfa-2a (with or without lamivudine) achieved a sustained response at end of follow-up (6 months post treatment) than patients treated with lamivudine monotherapy with respect to the coprimary end points of ALT normalization (59% and 60% vs. 44%, respectively;  $P = 0.003$ ) and HBV-DNA suppression (HBV DNA < 20,000 copies/ml) (43% and 44% vs. 29%, respectively;  $P = 0.005$ ) at week 72. The combined end point of ALT normalization and HBV-DNA suppression at the end of follow-up was achieved in 36%, 38%, and 23% ( $P = 0.004$ ) of patients receiving peginterferon alfa-2a, peginterferon alfa-2a plus lamivudine, and lamivudine, respectively. Five patients (3%) treated with peginterferon alfa-2a monotherapy, three (2%) treated with peginterferon alfa-2a plus lamivudine, and none treated with lamivudine showed HBsAg seroconversion at the end of follow-up [9].

Although peginterferon alfa-2a has improved clinical outcomes compared to lamivudine at defined treatment duration, the cost of 48 weeks of therapy is

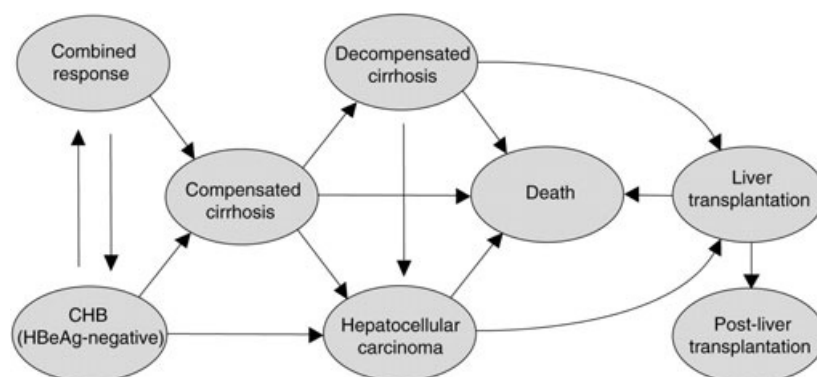
higher by 172,704 NTD. Thus, the question for health-care payers arises: Are the clinical benefits worth the additional cost? The objectives of this analysis were to model the long-term clinical and economic outcomes associated with peginterferon alfa-2a versus lamivudine treatment in HBeAg-negative CHB based on the results of the randomized clinical trial data, and to evaluate the relative cost-effectiveness of these two therapies from the Taiwan BNHI perspective.

## Methods

### Model Description

A Markov model of HBeAg-negative disease was utilized to forecast the long-term clinical and economic effects of peginterferon alfa-2a versus lamivudine for the treatment of HBeAg-negative CHB. The course of HBeAg-negative disease was represented as a sequence of transitions between mutually exclusive health states, each of which was defined by a patient's clinical condition. Associated with the health states were corresponding quality-of-life values and costs. The health states were defined to reflect CHB (starting health state), response, compensated cirrhosis, decompensated cirrhosis, HCC, liver transplantation, and death (Fig. 1). The model linked combined response rate (HBV-DNA suppression to HBV DNA < 20,000 copies/ml, and ALT normalization) at the end of follow-up (24 weeks post treatment) measured in Marcellin et al.'s phase III clinical study [9] to final outcomes, life-years gained, and quality-adjusted life-years (QALYs) gained [10]. A hypothetical cohort of patients with a mean age of 40 years was used in the model, based on the characteristics of HBeAg-negative CHB patients in the clinical trial [9]. Overall, the population used in the modeled evaluation is expected to be similar to the target population in Taiwan. This was confirmed by a local Taiwanese study performed in patients with HBeAg-negative CHB [11] and by local expert hepatologists.

The time horizon of the analysis extended over a patient's lifetime, and was divided into equal



**Figure 1** Structure of disease simulation model. Patients could move between health states in yearly cycles; all patients could experience non-HBV-related mortality. CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen.

increments of time (in this case, 1 year each), known as Markov cycles, during which patients “transition” from one health state to another [10]. In each 1-year cycle, patients with active CHB were at risk of developing compensated cirrhosis or HCC. Patients in the response state could spontaneously return to the CHB state, and had a small risk of progressing to compensated cirrhosis. Patients in the CHB state could also spontaneously move to the response state, although at a low rate. Patients who developed compensated cirrhosis faced a future risk of developing HCC or decompensated cirrhosis. Patients who developed decompensated cirrhosis could develop HCC or receive a liver transplantation. Finally, patients with HCC probably need liver transplantation and have an increased risk disease-related mortality. The liver transplantation health state was represented by two distinct health states: 1) the year in which the transplantation was received; and 2) the second and subsequent years after transplantation. For each 1-year cycle, patients faced competing mortality risks from complications related to CHB or other causes. Patients who achieved response were assumed to face the same mortality risk as healthy individuals. Age-specific standard life tables from 2002 were used to reflect the background risk of death from causes other than CHB in the general population [12]. The probability of YMDD mutation caused by lamivudine treatment and use of adefovir salvage therapy was not included in our analysis, as adefovir is not currently reimbursed by the BNHI. We also opted to be conservative and not take into account the occurrence of HBsAg seroconversion

with peginterferon alfa-2a therapy seen in Marcellin et al.’s study [9].

### Treatment Response and Disease Progression Estimates

The annual probabilities of moving between health states in the model were estimated based on a thorough review of the clinical literature, particularly publications based on Taiwanese patients, using MEDLINE (search 1950 to November 2004). In addition, we reviewed professional treatment guidelines and consensus statements, previously published economic models of CHB treatment, and input from a panel of eight hepatologists in Taiwan (Table 1) [5,7,9,11,13–24]. We used data from local Taiwanese publications whenever these data were available. In addition, a questionnaire compiled of transition rates reported in the medical literature was administered to the panel of eight expert hepatologists to ensure that the most appropriate estimates for Taiwanese patients with HBeAg-negative CHB were used in the model.

As discussed above, the estimates for sustained (6 months post treatment) combined treatment response (ALT normalization and HBV-DNA suppression) were derived from the randomized clinical trial comparing 48 weeks of peginterferon alfa-2a treatment to 48 weeks of lamivudine treatment [9]. The response rate for peginterferon alfa-2a was 36% for both the end of treatment (week 48) and the end of follow-up (week 72), and for lamivudine was 69% at the end of treatment and 23% at the end of follow-up (67% relapse). Nevertheless, additional treatment relapse may occur beyond that observed in the trial at 6 months follow-up. There are few data for lamivu-

**Table 1** Annual probabilities of transition between health states

Disease state from:	Disease state to:	Annual rate % (low–high)	Data source for base case
Combined response	CHB, 6th month to 12th month post lamivudine treatment	50 (40–60)	[20]
	CHB, 6th month to 12th month post peginterferon alfa-2a treatment	25 (15–35)	[9,11]
	CHB, spontaneous relapse	6 (3–10)	[22,24]
	Compensated cirrhosis	1.3 (1–2)	[13]
CHB	Compensated cirrhosis	9 (6–12)	[7]
	Hepatocellular carcinoma	0.83 (0.5–2)	[14]
	Spontaneous response	1.6 (1–3)	[11,24]
Compensated cirrhosis	Decompensated cirrhosis	5 (2.3–5.6)	[21]
	Hepatocellular carcinoma	7.1 (2.8–7.1)	[15]
	Death	5.1 (3.4–5.1)	[16]
Decompensated cirrhosis	Hepatocellular carcinoma	2.5 (2–8)	[21]
	Liver transplantation	1.4 (0.05–3.1)	[5,17]
	Death	39 (23.5–40)	[21]
Hepatocellular carcinoma	Liver transplantation	0.08 (0.02–0.08)	[18]
	Death	37.2 (37–56)	[23]
Liver transplantation	Post liver transplantation	85 (79–90)	[19]
	Death	15 (10–21)	[19]
Post-liver transplantation	Death, second year and beyond	1.5 (1–5.7)	[19]

Annual transition probabilities do not add to 1 because there is an annual probability to death from non-CHB-related causes and a residual probability of remaining in the same health state that are not listed here.  
CHB, chronic hepatitis B.

dine on relapse beyond 6 months, but several studies indicate that the 1–2 years post-treatment combined response rate is 11% to 20% [20,25,26]. We considered the studies by Santantonio et al. and Tassopoulos et al. to be most relevant for lamivudine, as they reported combined treatment response data at the end of treatment and the end of follow-up [20,25,26]. Santantonio et al. reported 83% relapse at 1 year follow-up and Tassopoulos et al. reported 83% relapse at 6 months follow-up. Based on these data, we assumed conservatively that the 1-year total relapse rate was 80%; to reproduce this value in the model, approximately 50% of the 23% of lamivudine patients with response at 6 months follow-up would need to relapse in addition to the 67% who relapsed in the first 6 months of follow-up ( $67\% + 0.5 \times 23\% = 78.5\%$ ). We thus assumed 50% of lamivudine patients who had combined response at 6 months relapsed by the end of year 1.

There are no data on long-term combined response for peginterferon alfa-2a, and few data for interferon alfa. One study suggested an additional 50% of interferon-treated patients relapse between 6 months and 32 months post treatment [11]. Nevertheless, given that there was no relapse at 6 months post treatment in the peginterferon alfa-2a arm in Marcellin et al.'s clinical study [9], we assumed an additional 25% relapse with peginterferon alfa-2a beyond 6 months post treatment.

A critical determinate of disease progression is the development of cirrhosis from CHB. The general perception of the clinical community seems to be that HBeAg-negative disease is more likely to progress to advanced liver disease than HBeAg-positive. For example, the European Association for the Study of the Liver consensus statement on hepatitis B estimated that 2.0% to 5.5% of HBeAg-positive patients progress to cirrhosis per year compared to 8% to 10% of HBeAg-negative patients [7]. Nevertheless, studies on which these estimates are based are few and relatively small, and patients who present with HBeAg-negative disease are more likely to be older (and thus have more advanced disease) [27–29]. We used 9% in our model and varied it from 6% to 12% in a sensitivity analysis. The remainder of the estimates for disease progression (e.g., from cirrhosis) were assumed to be relatively similar to those for HBeAg-positive disease [21–24,30].

### Quality of Life (Health State Utilities)

Estimates for the quality-of-life values (utilities) for each of the health states in the model were derived from previously published studies (Table 2). We assumed the utility values for the HBV health states were the same for HBeAg-positive and HBeAg-negative disease. Pwu and Chan obtained utilities by interviewing 12 Taiwanese hepatologists and 53

**Table 2** Utility values for hepatitis B-related disease states

Disease state	Utility value (low–high)
Combined response	1 (0.98–1) [23]
Chronic hepatitis B	0.95 (0.9–0.95) [23]
Compensated cirrhosis	0.9 (0.8–0.92) [23]
Decompensated cirrhosis	0.54 (0.5–0.65) [22]
Hepatocellular carcinoma	0.5 (0.3–0.5) [23]
Liver transplantation	0.5 (0.5–0.6) [31]
Post liver transplantation	0.7 (0.6–0.8) [31]

patients using the time trade-off technique (asking subjects to trade years of life with a lower quality of life for fewer years with a better quality of life) [23]. Based on input from our survey of local hepatologists, we chose to use a utility of 0.54 from a cost-effectiveness analysis by Wong et al. rather than 0.65 from Pwu and Chan, as the panel felt this value was more representative of the quality of life for patients in this health state [22,23]. Wong et al. derived this estimate from expert panel members who assessed their own utilities for being in each CHB-related health state using 1) the standard reference gamble (trading off years of future healthy life to avoid immediate certain death), and 2) the time trade-off technique, and taking an average of these results. Because previous studies in HBV have not estimated utilities for the liver transplantation and post-liver transplantation health states, we used values from a cost-effectiveness model of hepatitis C treatment [31].

### Health-Care Costs

The annual costs of CHB, compensated cirrhosis, and decompensated cirrhosis were based on the average level of medical resource utilization indicated from a questionnaire survey among local hepatologists. Unit costs from the Fee Schedule for Medical Service and Reference List for Drugs set by the BNHI were used to allocate costs to the medical resource use data [32].

The aggregated annual costs of managing these disease states are shown in Table 3. A 25% increase and decrease of the base-case cost for each disease state was tested in sensitivity analyses. We assumed the costs for the hepatitis B-related health states were the same for HBeAg-positive and HBeAg-negative disease.

**Table 3** Annual cost of managing chronic hepatitis B-related complications

Disease state	Total annual management cost per patient (low–high) (NTD)
Chronic hepatitis B	11,806 (8,855–14,758) [32]
Compensated cirrhosis	20,821 (15,616–26,026) [32]
Decompensated cirrhosis	44,431 (33,323–55,539) [32]
Hepatocellular carcinoma	96,510 (72,383–130,638) [33]
Liver transplantation	1,720,632 (1,290,474–2,150,790) [32,34]
Post liver transplantation	508,901 (381,676–636,126) [32]

NTD, New Taiwan Dollars.



**Table 4** Results of cost-effectiveness analysis

Treatment strategy	Total costs (NTD)	Life expectancy (year)	Discounted life expectancy (year)	Incremental cost-effectiveness ratio* (NTD/LY gained)	Discounted QALYs (year)	Incremental cost-effectiveness ratio* (NTD/QALY gained)
Peginterferon alfa-2a monotherapy (48 weeks)	389,375	15.32	11.45		10.57	
Lamivudine monotherapy (48 weeks)	232,382	14.66	11.07		10.12	
Difference	156,992	0.66	0.38	413,770	0.45	346,868

\*The difference in cost divided by the difference in LY or QALY for each strategy compared to the next-best strategy. LY, life-year; NTD, New Taiwan Dollars; QALY, quality-adjusted life-year.

The total annual costs of managing CHB and compensated cirrhosis were calculated based on the resource utilization data of managing the disease after drug therapy has been administered and has failed as reported by the hepatologists in the survey. The annual cost of managing decompensated cirrhosis was calculated by weighting the annual costs of diuretic-sensitive ascites, refractory ascites, variceal hemorrhage, and hepatic encephalopathy by the proportion of patients in each of these disease states. The proportion of patients with each complication in the decompensated cirrhosis disease state was also determined from the survey (diuretic-sensitive ascites: 4.43%; refractory ascites: 6.17%; variceal hemorrhage: 1.36%; hepatic encephalopathy: 0.5%). The cost for HCC was derived from a study by Wang on the financial burden of liver cancer in Taiwan [33]. Liver transplantation costs were estimated based on the cost of a liver transplantation surgical procedure and treatment costs to avoid infections [34]. Treatment costs were based on the weekly BNHI price of peginterferon alfa-2a 180 µg and lamivudine 100 mg daily [32]. In the base case we assumed, all patients received peginterferon alfa-2a 180 µg or lamivudine 100 mg for 48 weeks. Nevertheless, in the sensitivity analysis, we adjusted the cumulative peginterferon alfa-2a dose for 48 weeks treatment by approximately 10%, because the actual mean cumulative dose of peginterferon alfa-2a used in the peginterferon alfa-2a monotherapy arm of Marcellin et al.'s study [9] was less than the per protocol cumulative dose because of dose modifications.

### Analysis Methods

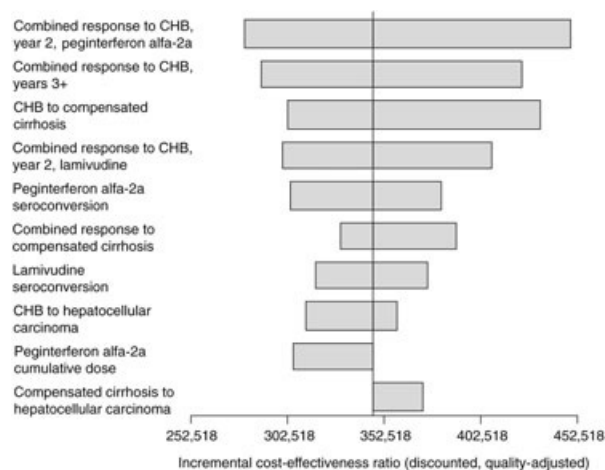
The comparative performance of alternative treatment strategies was depicted by the incremental cost-effectiveness ratio (ICER) (defined as the additional cost of a specific strategy, i.e., peginterferon alfa-2a, divided by its additional clinical benefit, compared to the next least expensive strategy, i.e., lamivudine) [35–37]. All costs and outcomes were discounted at a 3% annual rate. One-way sensitivity analyses were performed on all parameters in the model to identify results drivers and evaluate uncertainty in the model. In addition, although not requested by the Taiwan BNHI or included in the formal submission, a proba-

bilistic sensitivity analysis was performed. Beta distributions were assigned to probability and utility estimates, and normal distributions to cost estimates, based on the parameter ranges listed in Tables 1–3. Latin hypercube sampling was employed, and the convergence criteria were set to a change of less than 1% between successive simulations in the means and standard deviations of the model outcomes. The 95% central range of values for the ICER was determined and a cost-effectiveness acceptability curve generated.

### Results

The main results of our analysis are shown in Table 4. All costs are presented in NTD (1 USD = 31.96 NTD). Treatment with peginterferon alfa-2a resulted in total, discounted lifetime health-care costs associated with HBeAg-negative CHB of 389,375 NTD compared to 232,382 NTD for lamivudine, for a difference of 156,992 NTD. Peginterferon alfa-2a drug therapy was 172,704 NTD more expensive than lamivudine, but was offset by 15,711 NTD in savings of future medical care cost for CHB. The discounted life-years gained in the peginterferon alfa-2a arm was 11.45 years versus 11.07 years for lamivudine (a gain of 0.38). After adjustment for quality of life in the various HBV-related health states, peginterferon alfa-2a treatment resulted in 10.57 QALYs and lamivudine 10.12 QALYs. The increase in quality-adjusted life expectancy is 0.45 years with peginterferon alfa-2a at an additional cost of 156,992 NTD per person compared to lamivudine, yielding an ICER of 347,000 NTD (10,900 USD) per QALY gained.

As shown in the one-way sensitivity analyses in Figure 2, the ICER was most sensitive to variation in the relapse rate after peginterferon alfa-2a treatment was stopped, spontaneous relapse rate (relapse beyond second year of post-treatment), the probability of developing compensated cirrhosis from CHB, and the relapse rate after lamivudine treatment was stopped. Nevertheless, the ICER for peginterferon alfa-2a compared to lamivudine monotherapy ranged from 281,000 to 448,000 NTD per QALY gained despite independent variation in treatment efficacy, the health state transition probabilities, quality-of-life adjustments, and health state cost estimates in one-way



**Figure 2** Results of one-way sensitivity analyses: 10 most influential parameters. The width of the bars represents the high and low results obtained when each parameter was varied over the range in Table 1. CHB, chronic hepatitis B.

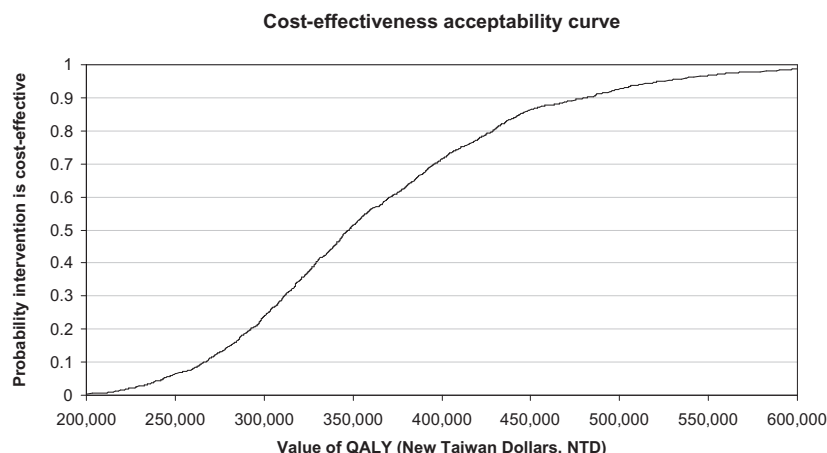
sensitivity analyses. A sensitivity analysis using the costs derived from a claims database analysis by Hsieh et al. increased the ICER to 361,000 NTD per QALY gained from the base-case value of 347,000 NTD per QALY gained [38]. The 95% central range from the probabilistic sensitivity analysis for the discounted incremental cost-utility ratio was 228,000–566,000 NTD (7100–17,700 USD). As shown in the cost-effectiveness acceptability curve, for example, the value placed on a QALY would have to be less than 350,000 NTD (11,100 USD) before the probability of the intervention being cost-effective was below 50% (Fig. 3).

## Discussion

The results of our analysis suggest that peginterferon alfa-2a therapy versus lamivudine treatment for

HBeAg-negative CHB in Taiwan provides incremental benefits in life expectancy and quality of life at an increased total cost that is within the range of commonly reimbursed medical interventions [23,39]. In the United States, 50,000 USD per QALY gained is commonly used as the cutoff value for an ICER when evaluating resource allocation, although this may range up to 100,000 USD per QALY gained accounting for inflation and currently reimbursed health-care interventions [37]. Although there is no consensus yet on an ICER cutoff value in Taiwan, the annual income per capita may serve as a guide. According to the Department of Statistics, Ministry of Economic Affairs in Taiwan, in 2003, GNP per capita was 13,156 USD in Taiwan compared to 37,939 USD in the United States. Therefore, an ICER of 17,300 USD per QALY gained  $[(13,156/37,939) \times 50,000 \text{ USD}]$ , equivalent to 553,000 NTD per QALY gained, is a potential approximate threshold for Taiwan, although additional data on the cost-effectiveness of currently reimbursed health-care technologies are needed. Thus, although reimbursement for peginterferon alfa-2a may present a budgetary challenge, our analysis suggests that such expenditure represents good value for money. The clinical implications of our analysis are also important. HBeAg-negative CHB is a difficult-to-treat disease, but because of the greater durable response with peginterferon alfa-2a compared to lamivudine, our analysis suggests that peginterferon alfa-2a offers significantly improved long-term outcomes.

No other published studies to date have evaluated the cost-effectiveness of peginterferon alfa-2a in the treatment of HBeAg-negative CHB. In a recent study, Kanwal et al. did evaluate the cost-effectiveness of 12 months of (nonpegylated) interferon alfa therapy versus chronic antiviral (lamivudine or adefovir) treatment for HBeAg-negative CHB [24]. The authors estimated that interferon alfa was cost-effective compared to lamivudine monotherapy, and in this regard the findings, albeit of different treatments, are consistent



**Figure 3** Cost-effectiveness acceptability curve. The curve represents the probability the intervention is cost-effective over the range of cost-effectiveness thresholds shown on the x-axis.

with ours. Kanwal et al. also reported that lamivudine treatment followed by adefovir salvage led to the greatest improvements in QALY. This finding is likely to be a result of the durable treatment response used for lamivudine-treated patients without resistance and for adefovir-treated patients: 10% per year for the duration of the simulation. As noted by the authors, there are little data for these estimates, and further clinical studies are needed.

Two previous studies have estimated the cost of managing CHB and its complications in Taiwan: Pwu and Chan in 2002 and Hsieh et al. in 2004 [23,38]. Pwu and Chan estimated costs from interviews with Taiwanese hepatologists (apparently from academic medical centers, as in our study) about common practice patterns for management of CHB, and from a hospital medical chart review. Hsieh et al. estimated costs based on the BNHI claims data from the year 2000. Of BNHI beneficiaries in Taiwan, 1% were randomly selected and observed for 1 year. During this 1-year period, the relevant cost of medical care for CHB or its complications (except liver transplantation) was collected. The medical costs of CHB and compensated cirrhosis in Hsieh et al.'s study are significantly lower than the costs used in our model and by Pwu and Chan. We speculate that patients at academic medical centers are more closely followed than patients in Hsieh et al.'s study and provided with more intensive medical care. The costs for decompensated cirrhosis and HCC are more comparable between our model and Hsieh et al.'s compared to that of Pwu and Chan. Despite these different cost estimates, a sensitivity analysis using the costs of Hsieh et al. increased the ICER to only 361,000 NTD per QALY gained from the base-case value of 348,000 NTD per QALY gained.

There are several important limitations of this study, primarily because of the paucity of long-term treatment and disease progression data for HBeAg-negative disease. In particular, the risk of progression to cirrhosis for patients with chronic HBeAg-negative HBV infection is not well understood. Nevertheless, we varied this estimate between 6% and 12% without a significant change in our results. Treatment relapse rates after the initial 6 months of follow-up were also important parameters in the model; we varied these from 15% to 35% for peginterferon alfa-2a and from 40% to 60% for lamivudine. Again, however, the ICER remained less than NTD 450,000.

Several key assumptions in our study were conservative, that is, favored lamivudine. We did not include lamivudine drug resistance in the model. Although we evaluated only 1 year of lamivudine treatment, resistance in the pivotal clinical trial at 1 year was 17%; patients experiencing resistance may have a higher likelihood of disease progression, and increased medical care costs, in part due to salvage treatment

with adefovir. We also assumed lamivudine-treated patients continued to receive some, although diminishing, benefit once treatment was stopped. We did not include HBsAg seroconversion, considered clinically to be the closest to a "cure" in the model, although the HBsAg seroconversion observed in the clinical trial was 3% to 4% for peginterferon alfa-2a-treated patients versus 0% for lamivudine-treated patients [9].

In summary, our analysis suggests that in HBeAg-negative CHB, 48 weeks of treatment with peginterferon alfa-2a compared to 48 weeks of lamivudine offers life expectancy and quality-of-life improvements at a favorable cost-effectiveness ratio. Additional studies evaluating the long-term disease and treatment outcomes in HBeAg-negative CHB will be valuable for assessing the clinical utility and economic value of treatments for this challenging disease

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